The gamma catenin/CBP complex maintains survivin transcription in beta-catenin deficient/depleted cancer cells.

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Public Summary:
The identification of novel therapeutic regimens for Imatinib resistant CML is a critical issue. This work demonstrates that the ability of the small molecule ICG-001 to block the CBP/✚-catenin interaction in addition to the CBP/β-catenin interaction may be clinically significant in the treatment of cancers, including CML, in which ✚-catenin substitutes for reduced nuclear β-catenin, either due to genetic deletion or pharmacologic reduction of nuclear β-catenin.

Scientific Abstract:
Previously, we demonstrated that survivin expression is CBP/beta-catenin/TCF-dependent. Now, using NCI-H28 cells, which harbor a homozygous deletion of beta-catenin, we demonstrate that survivin transcription can similarly be mediated by nuclear gamma-catenin. ICG-001, a specific inhibitor of binding to the N-terminus of CBP, effectively attenuates survivin expression. We demonstrate that gamma-catenin by binding to TCF family members and specifically recruiting the coactivator CBP drives survivin transcription particularly in beta-catenin-deficient cells. We also examined the relative expression of gamma-catenin and beta-catenin in 90 cases of chronic myeloid leukemia (CML) in a published gene expression microarray data base. A statistically significant negative correlation between gamma-catenin and beta-catenin was found in AP/BC cases (-0.389, P = 0.006). Furthermore, in subsequent independent validation studies by qPCR in 28 CP and BC patients increased gamma-catenin expression predominated in BC cases and was associated with concomitantly increased survivin expression. Gene expression was 3- and 6-fold greater in BC patients as compared to CP patients, for gamma-catenin and survivin, respectively. Consistent with this observation, nuclear gamma-catenin accumulation was evident in this population consistent with a potential transcriptional role. Combined treatment with imatinib mesylate (IM) and ICG-001 significantly inhibited colony formation in sorted CD34(+) CML progenitors (survivin(+)/gamma-catenin(high)/beta-catenin(low)) isolated from one BC and one AP patient resistant to IM. Therefore, we believe that the ability of ICG-001 to block both the CBP/gamma-catenin interaction and the CBP/beta-catenin interaction may have clinical significance in cancers in which gamma-catenin plays a significant transcriptional role.